Nonpharmacologic Therapies in Patients With Exacerbation of Chronic Obstructive Pulmonary Disease: A Systematic Review With Meta-Analysis

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Authors: Claudia C. Dobler, MD, PhD; Allison S. Morrow, BA; Magdoleen H. Farah, MBBS; Bradley Beuschel, BSPH; Adbul M. Majzoub, MD; Michael E. Wilson, MD; Basahar Hasan, MD; Mohamed O. Seisa, MD; Lubna Daraz, PhD; Larry J. Prokop MLS; Hassan Murad, MD, MPH; Zhen Wang, PhD

eTable 1. Search strategy

We searched Embase, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Cochrane Central Registrar of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus from database inception to January 2, 2019. We additionally searched FDA, ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency (MHRA), AHRQ's Horizon Scanning System, conference proceedings, patient advocate group websites, and medical society websites. Reference mining of identified publications was used to identify additional relevant publications. The search strategy was developed and executed by an experienced medical librarian (L.J.P.) and peer-reviewed by an independent librarian. Details of the search strategies are listed below.

Ovid

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials November 2018, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 28, 2018, Embase 1974 to 2018 January 02, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to January 02, 2019

Search Strategy:

Searches

1 exp Pulmonary Disease, Chronic Obstructive/dh, dt, px, rh, th or exp Lung Diseases, Obstructive/dh, dt, px, rh, th

2 exp chronic obstructive lung disease/dm, dt, rh, th

3 ((chronic* adj3 bronchiti*) or (obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) or aecb or "chronic airflow disease*" or "chronic airflow disorder*" or "chronic airflow limitation*" or "chronic airflow obstruction*" or "chronic airway disease*" or "chronic airway disorder*" or "chronic airway limitation*" or "chronic airway obstruction*" or "chronic bronchitis" or "chronic obstructive airflow disease*" or "chronic obstructive airflow disorder*" or "chronic obstructive airway disease*" or "chronic obstructive airway disorder*" or "chronic obstructive bronchitis" or "chronic obstructive bronchopulmonary disease*" or "chronic obstructive broncho-pulmonary disease*" or "chronic obstructive bronchopulmonary disorder*" or "chronic obstructive broncho-pulmonary disorder*" or "chronic obstructive lung disease*" or "chronic obstructive lung disorder*" or "chronic obstructive pulmonary disease*" or "chronic obstructive pulmonary disorder*" or "chronic obstructive respiratory disease*" or "chronic obstructive respiratory disorder*" or coad or cobd or copd or emphysema* or "obstructive lung disease" or "obstructive lung disorder*" or "obstructive pulmonary disease*" or "obstructive pulmonary disorder*" or "obstructive pulmonary tract disease*" or "obstructive pulmonary tract disorder*" or "obstructive respiratory disease*" or "obstructive respiratory disorder*" or "obstructive respiratory tract disease*" or "obstructive respiratory tract disorder*").ti,ab,hw,kw.

4 ((increas* adj3 (severity or seriousness)) or exacerbation* or worsen*).ti,ab,hw,kw.

5 (1 or 2 or 3) and 4

6 exp Bronchodilator Agents/ or exp Adrenergic beta-2 Receptor Agonists/ or exp Cholinergic Antagonists/ or exp Phosphodiesterase 4 Inhibitors/ or exp Antibiotic Prophylaxis/ or exp Anti-Bacterial Agents/ or exp antibiotic agent/ or exp Benzodiazepines/ or exp Respiration, Artificial/ or exp Adrenal Cortex Hormones/ or exp corticosteroid/ or exp corticosteroid therapy/ or exp Expectorants/ or exp narcotic analgesic agent/ or exp Analgesics, Opioid/ or exp Smoking Cessation/ or exp Respiratory Therapy/ or exp exercise/ or exp Exercise

Therapy/ or exp Breathing Exercises/ or exp Exercise Movement Techniques/ or exp Nutrition Therapy/ or exp Influenza Vaccines/ or exp Pneumococcal Vaccines/ or exp vaccination/ or exp Psychotherapy/ or exp Cognitive Therapy/ or exp Cognitive Behavior Therapy/ or exp Mindfulness/ or exp Mind-Body Therapies/ or exp Self Care/ or exp Acupuncture exp Complementary Therapies/ or exp Electric Stimulation Therapy/

7 ((action adj3 plan*) or (disease adj2 manag*) or (management adj1 program*) or Acupuncture or "Adrenal Cortex Hormone*" or "Adrenergic beta-2 Receptor Agonist*" or "Adrenergic beta-2 Receptor Antagonist*" or "alternative medicine*" or antibacterial* or "Anti-Bacterial*" or antibiotic* or Anticholinergic* or "artificial respiration" or behavior* or behaviour* or Benzodiazepine* or "Beta adrenergic agonist*" or "Beta adrenergic Antagonist*" or "Breathing Exercise*" or Bronchodilator* or chemotherap* or "Chest physiotherap*" or "Cholinergic agonist*" or "Cholinergic Antagonist*" or "Cognitive Behavior Therap*" or "Cognitive Therap*" or "Complementary Therap*" or corticosteroid* or diet or drug* or educat* or "Electric Stimulation*" or empower* or exercise* or Expectorant* or Glucocorticoid* or instruct* or "management plan*" or "Mind-Body" or Mindfulnes* or narcotic* or Nutrition* or opioid* or "Oxygen therap*" or "patient cent*" or "patient educat*" or "patient focus*" or pharmacotherap* or "Phosphodiesterase 4 Inhibitor*" or Psychotherap* or respirator* or "Respiratory Therap*" or "Self Car*" or "self-efficac*" or "self-manag*" or "Smoking Cessation" or steroid* or train* or Vaccin* or ventilation or ventilator*).ti,ab,hw,kw.

8 6 or 7

9 5 and 8

10 limit 9 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in CCTR,CDSR,Embase; records were retained]

11 limit 10 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in CCTR,CDSR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]

12 limit 9 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") [Limit not valid in CCTR,CDSR,Embase; records were retained]

13 limit 12 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) [Limit not valid in CCTR,CDSR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]

14 13 not 11

15 9 not 14

16 limit 15 to (editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in CCTR,CDSR,Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]

17 from 16 keep 8-93

18 (15 not 16) or 17

19 limit 18 to yr="2017 -Current"
20 limit 19 to yr="2018 -Current"
21 remove duplicates from 20
22 19 not 20
23 remove duplicates from 22
24 21 or 23
25 exp meta analysis/
26 exp Meta-Analysis as Topic/
27 exp "systematic review"/
28 ((meta adj analys*) or (systematic* adj3 review*)).mp,pt.
29 25 or 26 or 27 or 28
30 24 and 29
31 exp controlled study/
32 exp Randomized Controlled Trial/
33 exp triple blind procedure/
34 exp Double-Blind Method/
35 exp Single-Blind Method/
36 exp latin square design/
37 ((control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square").mp,pt.
38 or/31-37
39 (24 not 30) and 38

Scopus

1 TITLE-ABS-KEY((chronic* W/3 bronchiti*) or (obstruct* W/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) or aecb or "chronic airflow disease*" or "chronic airflow disorder*" or "chronic airflow limitation*" or "chronic airflow obstruction*" or "chronic airway disease*" or "chronic airway disorder*" or "chronic airway limitation*" or "chronic airway obstruction*" or "chronic bronchitis" or "chronic obstructive airflow disease*" or "chronic obstructive airflow disorder*" or "chronic obstructive airway disease*" or "chronic obstructive airway disorder*" or "chronic obstructive bronchitis" or "chronic obstructive bronchopulmonary disease*" or "chronic obstructive broncho-pulmonary disease*" or "chronic obstructive bronchopulmonary disorder*" or "chronic obstructive broncho-pulmonary disorder*" or "chronic obstructive lung disease*" or "chronic obstructive lung disorder*" or "chronic obstructive pulmonary disease*" or "chronic obstructive pulmonary disorder*" or "chronic obstructive respiratory disease*" or "chronic obstructive respiratory disorder*" or coad or cobd or copd or emphysema* or "obstructive lung disease" or "obstructive lung disorder*" or "obstructive pulmonary disease*" or "obstructive pulmonary disorder*" or "obstructive pulmonary tract disease*" or "obstructive pulmonary tract disorder*" or "obstructive respiratory disease*" or "obstructive respiratory disorder*" or "obstructive respiratory tract disease*" or "obstructive respiratory tract disorder*")
2 TITLE-ABS-KEY((increas* W/3 (severity or seriousness)) or exacerbation* or worsen*)

3 TITLE-ABS-KEY((action W/3 plan*) or (disease W/2 manag*) or (management W/1 program*) or Acupuncture or "Adrenal Cortex Hormone*" or "Adrenergic beta-2 Receptor Agonist*" or "Adrenergic beta-2 Receptor Antagonist*" or "alternative medicine*" or antibacterial* or "Anti-Bacterial*" or antibiotic* or Anticholinergic* or "artificial respiration" or behavior* or behaviour* or Benzodiazepine* or "Beta adrenergic agonist*" or "Beta adrenergic Antagonist*" or "Breathing Exercise*" or Bronchodilator* or chemotherap* or "Chest physiotherap*" or "Cholinergic agonist*" or "Cholinergic Antagonist*" or "Cognitive Behavior Therap*" or "Cognitive Therap*" or "Complementary Therap*" or corticosteroid* or diet or drug* or educat* or "Electric Stimulation*" or empower* or exercise* or Expectorant* or Glucocorticoid* or instruct* or "management plan*" or "Mind-Body" or Mindfulnes* or narcotic* or Nutrition* or opioid* or "Oxygen therap*" or "patient cent*" or "patient educat*" or "patient focus*" or pharmacotherap* or "Phosphodiesterase 4 Inhibitor*" or Psychotherap* or respirator* or "Respiratory Therap*" or "Self Car*" or "self-efficac*" or "self-manag*" or "Smoking Cessation" or steroid* or train* or Vaccin* or ventilation or ventilator*)
4 1 and 2 and 3
5 TITLE-ABS-KEY(newborn* or neonat* or infant* or toddler* or child* or adolescent* or paediatric* or pediatric* or girl or girls or boy or boys or teen or teens or teenager* or preschooler* or "pre-schooler*" or preteen or preteens or "pre-teen" or "pre-teens" or youth or youths) AND NOT TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged" OR elderly OR geriatric* OR "old people" OR "old person*" OR "older people" OR "older person*" OR "very old")
6 4 and not 5
7 DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
8 6 and not 7
9 PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
10 8 and not 9
11 TITLE-ABS-KEY("consensus development" or guideline* or "position statement*")
12 10 and not 11
13 TITLE-ABS-KEY((meta W/1 analys*) or (systematic* W/3 review*))
14 12 and 13
15 12 and not 14
16 TITLE-ABS-KEY((control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square")
17 15 and 16

ClinicalTrials.Gov

(aecb OR "airflow obstruction" OR "airway obstruction" OR "bronchial obstruction" OR "bronchus obstruction" OR "chronic airflow disease") AND ("increased severity" OR "increasing severity"
OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("chronic airflow disorder" OR "chronic airflow limitation" OR "chronic airflow obstruction" OR "chronic airway disease" OR "chronic airway disorder" OR "chronic airway limitation") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("chronic airway obstruction" OR "chronic bronchitis" OR "chronic obstructive airflow disease" OR "chronic obstructive airflow disorder" OR "chronic obstructive airway disease" OR "chronic obstructive airway disorder") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("chronic obstructive bronchitis" OR "chronic obstructive bronchopulmonary disease" OR "chronic obstructive broncho-pulmonary disease" OR "chronic obstructive bronchopulmonary disorder") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("chronic obstructive broncho-pulmonary disorder" OR "chronic obstructive lung disease" OR "chronic obstructive lung disorder" OR "chronic obstructive pulmonary disease" OR "chronic obstructive pulmonary disorder") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("chronic obstructive respiratory disease" OR "chronic obstructive respiratory disorder" OR coad OR cobd OR copd OR emphysema OR "lung obstruction" OR "obstructive lung disease" OR "obstructive lung disorder") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("obstructive pulmonary disease" OR "obstructive pulmonary disorder" OR "obstructive pulmonary tract disease" OR "obstructive pulmonary tract disorder" OR "obstructive respiratory disease") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("obstructive respiratory disorder" OR "obstructive respiratory tract disease" OR "obstructive respiratory tract disorder" OR "pulmonary obstruction" OR "respiratory obstruction") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

All limited to adults.

eTable 2. Categories of adverse events

Type of adverse events	Example
Allergy and Immunology adverse event	Dermatitis
Cardiovascular adverse event	Paroxysmal atrial fibrillation, atrial fibrillation, , palpitations, arrhythmia, symptomatic sinus, tachycardia
Dermatological adverse event	Rash, urticaria, exanthema, pruritus
Ear, nose and throat adverse event	Transient episode of vocal cord dysfunction
Endocrine adverse event	Hyperglycemia, metabolism and nutrition disorders
Gastrointestinal adverse event	Gastrointestinal bleeding, diarrhea, nausea, stomachache, epigastric pain, heartburn, vomiting, constipation
General Internal Medicine adverse event	Facial puffiness, dizziness, new or worse hypertension, fatigue, chills, insomnia,, flushing, confusion, fever
Hepatic adverse event	Increased aspartate aminotransferase
Infectious (non-respiratory) adverse event	Vaginitis, urinary tract infection, influenza
Musculoskeletal adverse event	Muscle cramps, myalgia, tendonitis, rigors, musculoskeletal pain, muscle soreness
Neurological adverse event	Tremor, headache, seizure, rigors
Ocular adverse event	Blurred vision
Oncological adverse event	Classified as malignancy-related AEs by authors of the original study
Psychiatric adverse event	Mood change, psychosis, nervousness
Respiratory adverse event	Shortness of breath, respiratory acidosis, requiring noninvasive mechanical ventilation, dyspnea, bronchitis, wheezing, pneumothorax and pneumomediastinum, pneumonia, worsening exacerbation of COPD, bronchospasm
Urogenital adverse event	Hematuria

eTable 3. Definitions of Strength of Evidence

Strength of Evidence (SOE)	Definition
High	Confident that the estimate of effect lies close to the true effect (the body of evidence has few or no deficiencies and judged to be stable).
Moderate	Moderately confident that the estimate of effect lies close to the true effect (the body of evidence has some deficiencies and is judged to be likely stable)
Low	Limited confidence that the estimate of effect lies close to the true effect (the body of evidence has major or numerous deficiencies and is likely unstable)
Insufficient	No evidence, were unable to estimate an effect, or had no confidence in the estimate of effect)

eTable 4. Baseline characteristics of included studies

Author, Year	Country, Study Period, Setting	COPD Definition	COPD Exacerbation	Intervention(s) and comparison	Dose and Duration	COPD Severity (% predicted unless specified)	Patient Characteristics
Austin, 2010[1]	Australia, Ambulance to hospital	Patient reported history of COPD or emphysema or greater than 10 pack year history of smoking.	Paramedics at the site of the emergency Determined the diagnosis on the basis of appropriate acute symptoms, a history of chronic obstructive pulmonary disease (or emphysema) from the patient, or a greater than 10 pack year history of smoking.	High Flow/Free Flow Oxygen	8-10liters/min during ambulance ride and up to 30 mins in the ER (until blood gas analysis was taken)	FEV1: Mean 42.1±16.4	117 patients aged 68±10.2 years, 51% female
				Titrated Oxygen	During ambulance ride and up to 30 mins in the ER (until blood gas analysis was taken)	FEV1: Mean 43.3±16.5	97 patients aged 67.9±10.3 years, 54% female
Basri, 2017[2]	Pakistan, Inpatient hospital floor	Clinical diagnosis	Clinical diagnosis, hospital admission	Management without Chest Physiotherapy		NR	30 patients aged 53±3.7 years, 40% female
				Chest Physiotherapy	For 14 days.	NR	30 patients aged 55±3.8 years, 56% female
Behnke, 2000[3]	Germany , Inpatient hospital floor	Severe COPD according to international guidelines	Hospital admission	Aerobic Exercise	10 day walking training program in hospital followed by 60 day at home	FEV1: Mean 34.1± 7.4	23 patients aged 64.0±1.9 years, 20% female
				Management without Aerobic Exercise		FEV1: Mean 37.5±6.6	23 patients aged 68.0±2.2 years, 27% female
Borges, 2014[4]	Brazil, Inpatient hospital floor	FEV1/FVC ≤ 0.7	Increase in sputum or cough or worsening of dyspnea, hospital admission	Resistance Training	A minimum of 3 sessions of whole-body resistance training program over 3 days.	FEV1: Mean 41.7±13.6	21 patients aged 64.1±12.5 years, 29% female

				Management without Resistance Training		FEV1: Mean 39.1±15.5	25 patients aged 67.8±9 years, 47% female
Brown, 1987[5]*	Canada, Outpatient, Inpatient hospital floor	Chronic productive cough with at least 30 ml of sputum production daily	Acute episode of pneumonia or increase in sputum production to at least 30 ml of sputum production daily	Chest Wall Vibration	Mechanical vibration for 15 mins on day 1. Positioning on day 2 over 2 days.	FEV1: Mean 33.4±17.5	12 total patients aged 66.5±11.5 years, 29% female
				Positioning	Positioning on day 1. Mechanical vibration for 15 mins on day 2 over 2 days.		
Cox, 2018[6]	United Kingdom 09/2015 to 04/2016, Outpatient, Inpatient hospital floor	Admission to hospital with primary diagnosis of AECOPD (clinically determined by treating physician, pH >7.35, unstable hypoxemia excluded	Clinical diagnosis, hospital admission	Management without Early Pulmonary Rehabilitation	Four exercise sessions over 14 days in the patient's home	NR	15 patients aged 67.8±11.12 years, 67% female
				Early Rehabilitation	16 revolutions of the bike on both set of limbs, three times a day for 5 consecutive days	NR	15 patients aged 67.8±11.12 years, 60% female
Cross, 2012[7]	United Kingdom 11/2005 to 4/2008, Inpatient hospital floor	Clinical diagnosis	Clinical diagnosis, hospital admission	Manual Chest Physiotherapy	Active Cycle of Breathing Technique: Mean: 2.53 sessions/ 11.9 mins per session	NR	258 patients aged 69.08±9.85 years, 44.57% female
				Management without Manual Chest Physiotherapy		NR	264 patients aged 69.58±9.51 years, 41.29% female

Eaton, 2009[8]	New Zealand 06/2005 to 10/2006, Inpatient hospital floor Inpatient hospital floor	ATS/ERS criteria	Exertional dyspnea interfering with daily activity, hospital admission	Early Pulmonary Rehabilitation	1-h sessions of supervised exercise training, twice weekly for 56 days.	FEV1: Mean 36±16 0.8±0.4 L	47 patients aged 70.1±10.3 years, 55% female
				Management without Early Rehabilitation		FEV1: Mean 35±16 0.8±0.4 L	50 patients aged 69.7±9.4 years, 58% female
Goktalay, 2013[9]	Turkey 04/2009 to 07/2011, Inpatient hospital floor	GOLD stage 3-4	Increased dyspnea, increased cough and sputum production, altered sputum color and/or viscosity, fever and radiologic consolidation, hospital admission	Management without High-frequency Chest Wall Oscillation Therapy		FEV1: Mean 30±8.93	25 patients aged 66.52 ±6.59, 2% female
				High-frequency Chest Wall Oscillation Therapy	20 mins, 3x/24hrs (total of 60 mins) for 5 days Application and oscillation frequency were standardized at 20 Hz and 10 Hz	FEV1: Mean 28±8.95	25 patients aged 63.6±7.99, 2% female
Greening, 2014[10]	United Kingdom, Inpatient hospital floor	COPD diagnosis, MRC dyspnea 3 or greater	NR	Early Pulmonary Rehabilitation	Daily timed walks and Daily strength training, comprising three sets of eight repetitions resistance training exercises with weights for 10 days.	N/A	169 patients
				Management without Early Rehabilitation		N/A	151 patients

Greulich, 2014[11]	Germany 10/2010 to 07/2012, Inpatient hospital floor	NR	NR, hospital admission	Management without Whole Body Vibration	Standard program: 5 min mobilization, 5 min passive movement, and 10 min respiratory exercises	FEV1: Mean 38.4±17.82	26 patients aged 70.4±10.1 years, 40% female
				Whole Body Vibration	Standard program: 5 min mobilization, 5 min passive movement, and 10 min respiratory exercises complemented with sessions on the WBV device	FEV1: Mean 32.71±13.18	23 patients aged 66.4±9.93 years, 30% female
He, 2015[12]	China 12/2011-11/2013, Inpatient hospital floor	GOLD criteria	The worsening of respiratory symptoms beyond normal day-to-day variation and leading to a change in medication, MMRC > 0, and hospital admission	Early Pulmonary Rehabilitation	Each PR session included exercise training, relaxation, breathing retraining and education (from the second day of admission until discharge) for a mean of 10 days	FEV1: Mean: 38±16.7	66 patients aged 69.2±12.4 9.1% female
				Management without Early Rehabilitation	Mean of 10 days	FEV1: Mean: 39±27.8	28 patients aged 73.9±9.7, 17.6% female
Kirsten, 1998[13]	Germany, Inpatient hospital floor	International guidelines	Hospitalization	Aerobic Exercise	6-min treadmill walking test and five walking sessions per day for 10 days	NR	15 patients aged 65.5±11.8
				Management without Aerobic Exercise		NR	14 patients aged 62.3±9.1

Kodric, 2009[14]	Italy 03/2002-09/2002, Inpatient hospital floor	GOLD criteria	Clinical history, physical examination, chest x-ray, severity score according to the Anthonisen Criteria	Management without Chest physiotherapy technique		FEV1: Mean 52.3±18.7	29 patients aged 69.1±8.3, 33% female
				Chest physiotherapy technique ELTGOL (expiration with the glottis open in the lateral posture)	For 7 days	FEV1: Mean 55.6±27.6	30 patients aged 71.3±8.4, 28% female
Kurzaj, 2013[15]	Poland, Inpatient hospital floor	NR	Worsening COPD symptoms, hospital admission	Specialized Physiotherapy	Series of 6 massages, each lasting for 30 mins for 7 days.	NR	20 patients aged 57±5.7, 45% female
				Management without Specialized Physiotherapy		NR	10 patients aged 55±4.2, 30% female
Lellouche, 2016[16]	Canada 08/2011-02/2015, Inpatient hospital floor	Clinical diagnosis, at least 10 pack year smoking history	Clinical diagnosis, hospital admission	Free02 device oxygen titration, 0-20 L/min	Oxygen flow 0-20 liters /min	FEV1 in a stable state: Mean 40±11	25 patients aged 71±8, 46% female
				Manual Oxygen Titration		FEV1 in a stable state: Mean 51±20	25 patients aged 73±8, 46% female
Liao, 2015[17]	Taiwan, Inpatient hospital floor	NR	An increased need for medication and feel the need to seek additional medical assistance, hospital admission	Early Pulmonary Rehabilitation	RP sessions were conducted a minimum of twice per day for 10 mins per session for 4 days.	NR	31 patients aged 68 (44-89), 46.7% female
				Management without Early Rehabilitation	Usual care and health education for 4 days.	NR	31 patients aged ±, 32.3% female

Ogasawara, 2018[18]	Japan, Inpatient hospital floor	According to the GOLD criteria, not otherwise specified	The acute worsening of respiratory symptoms, which leads to the requirement of additional therapy	Omega-3 fatty acid enriched diet (Eicosapentaenoic acid)	1g, 1x/24 hours (total of 1g/24 hours)	FEV1: mean: 64.2± 24.7	25 patients aged 77.4±9.7 years, 12% female
				Usual Diet	1g, 1x/24 hours (total of 1g/24 hours)	FEV1: mean: 68.2±34.8	25 patients aged 79.1±7 years, 5% female
Oncu, 2017[19]	Turkey 8/2013-5/2014, Inpatient hospital floor	Clinical diagnosis	Worsening pulmonary function testing, hospital admission	Transcutaneous Electrical Nerve Stimulation, 45 min/day	20 sessions (TENS device) each for 45 minute application once a day for 20 days.	NR	41 patients, 20% female
				Management without Transcutaneous Electrical Nerve Stimulation	20 sessions (TENS device without electrical output) each for 45- minute application once a day for 20 days.	NR	41 patients, 25.7% female
Osadnik, 2014[20]	Australia 08/2010-01/2013, Inpatient hospital floor	NR	NR, hospital admission	Management without Positive Expiratory Pressure		FEV1: Mean 44.4±20.2	46 patients aged 69.5±9.8, 37.8% female
				Positive Expiratory Pressure	3session/ day, (five repetitions for each session, as tolerated for approximately 20 mins duration, one session was supervised), daily therapy continued until hospital discharge or 24 h without sputum expectoration, whichever came first	FEV1: Mean 37.3±19.7	46 patients aged 67.8±11.6, 33.3% female
Pourrashid, 2018[21]	Iran 12/2015-10/2016,	Post-bronchodilator FEV1/FVC <0.7,	Clinical diagnosis, hospital admission	Placebo	Single injection	Moderate: 31.3% Severe: 68.8%	35 patients aged 64.06±8.77, 15.6% female

	Inpatient hospital floor	post-bronchodilator FEV1 <80% predicted		Vitamin D, 300000 IU	Single injection of 300,000 IU	Moderate: 33.3% Severe: 66.7%	35 patients aged 62.73±8.26, 16.67% female
Sanjari, 2015[22]	Iran, Inpatient hospital floor	ERS criteria (FEV1 <88 % for men, <89 % for women)	A dramatic degradation of COPD symptoms (for example, the quantity and the color of phlegm or shortness of breath) that last for a couple of days, ED evaluation	Placebo	Daily for 7 days	NR	45 patients aged 58.4±9.5, 30.8% female
				Vitamin D	50000 IU, 1x/24hrs (total of 50000IU/24hrs) for 7 days	NR	45 patients aged 55.8±9.5, 28.6% female
				Calcitriol	0.25µg, 1x/24hrs (total of 0.25µg/24hrs) for 7 days	NR	45 patients aged 55.6±8.9, 12.8% female
Saudny-Unterberger, 1997[23]	Canada 11/1993 05/1996, Inpatient hospital floor	Clinical diagnosis of, and a FEV1 that was equal or less than 60% predicted	NR	Nutritional Support	An additional 10 kcal/kg/day for 14 days.	FEV1: Mean 33.21±3.57	17 patients aged 69.21±8.30, 43% female
				Usual Diet	Usual feeding for 14 days.	FEV1: Mean 34.70±4.42	14 patients aged 69.40±12.4, 30% female
Tang, 2012[24]	Australia 7/2009 8/2010, Inpatient hospital floor	Admitted to hospital with primary diagnosis of AECOPD	NR	Low-intensity Exercise Group	15-minute exercise sessions 2 times a day: walking at 40% of 3-min walk test for 7.5 min and completing 2 sets of an upper and lower limb resistance exercise with elasticized bands at each session	FEV1: Mean 45.1±18.6	11 patients aged 68±10.1, 55% female

				Moderate to high-intensity exercise group	15-minute exercise sessions 2 times a day: walking at 70% of their 3-minute walk test for 7.5 mins and completing 2 sets of an upper and lower limb resistance exercise with elasticized bands at each session	FEV1: Mean 46.1±18.3	10 patients aged 73.6±10, 80% female
				Management without Exercise Training	Once-daily physical therapy, including sputum clearance techniques, mobility assessments, and functional training required for safe discharge	FEV1: Mean 46.8±20.4	11 patients aged 78±8.8, 45% female
Torres-Sanchez, 2017[25]	Spain 12 /2013 07/2014, Inpatient hospital floor	Clinical diagnosis	American Thoracic Society criteria, hospital admission	Resistance Training	Cycling exercise intervention using a pedal exerciser	FEV1: Mean 42.35±10.62	29 patients aged 75.65±6.25 24.13% female
				Management without Exercise Training	Standard Care	FEV1: Mean 39.12±12.06	29 patients aged 72.12±8.19, 31% female
Torres-Sanchez, 2017[26]	Spain 9/2015 6/2016, Inpatient	GOLD criteria not otherwise specified	Clinical diagnosis, hospital admission	Management without Exercise Training	Standard medical treatment for 9 days.	FEV1: Mean 30.39±10.76	30 patients aged 71.13±9.39, 20% female

	hospital floor			Controlled breathing + Range of motion exercises	Daily 30-40min sessions of physical therapy (relaxation, pursed lips breathing, active expiration) plus active range of motion exercises for 9 days.	FEV1: Mean 31.26±5.33	30 patients aged 75.07±8.71, 6.7% female
				Resistance Training	A 5-min warm-up starting at a low and progressively increased the resistance of the elastic bands and the repetitions performed. Global movements of upper and lower limbs were performed against resistance during 30–40 min in individual supervised sessions. The number of repetitions was adapted to the subject's response taken into account the perceived dyspnea and fatigue during the exercise performance for 9 days,	FEV1: Mean 30.13±8.26	30 patients aged 70.12±10.6, 13.3% female
Troosters, 2010[27]	Belgium 01/2004 03/2005, Inpatient hospital floor	FEV1/FVC <70%	Clinical diagnosis, hospital admission	Management without Resistance Training	Standard doses of oral corticosteroids to treat the exacerbation for 7 days.	FEV1: Mean 50±18	20 patients aged 69±7, 26% female

				Resistance Training	3 sets of 8 repetitions quadriceps resistance training once a day for 7 days	FEV1: Mean 40±12	20 patients aged 67±8, 24% female
Tumer, 2009[28]	Turkey, Inpatient hospital floor	American Thoracic Society criteria	Increase, in at least two of the three following symptoms: dyspnea, cough and sputum production, hospital evaluation	Usual Diet	Standard hospital diet, 1800 kcal/day for 10 days.	NR	15 patients aged 63.6±4.3, 0% female
				High-fat Low-carbohydrate Diet	50% hospital diet and 50% a specific enteral product (pulmocare and hospital diet composed of 50% fat and 28% CHO) for 10 days.	NR	15 patients aged 60.9±7, 0% female
Vermeeren, 2004[29]	Netherlands, Inpatient hospital floor	GOLD criteria	Recent increase in breathlessness, cough and sputum production of sufficient severity to warrant hospital admission	Nutritional Intervention	Respifors: 125mL, 3x/24hours (total of 375mL/24hours) 2.38 MJ/day, 20 energy% protein, 20 energy% fat and 60 energy% carbohydrate for 9 days.	NR	23 patients aged 66±8, 39% female
				Placebo(non-caloric fluid, vanilla flavored water)	Vanilla flavored water: 125mL, 3x/24hours (total of 375mL/24hours) with 0 MJ/day for 9 days.	NR	24 patients aged 65±10, 25% female

Yohannes, 2003[30]	United Kingdom, Inpatient hospital floor	FEV1 <70% predicted together with a <20% improvement in FEV1 following standard doses of beta agonist by inhalation or nebulization.	Clinical diagnosis	Gutter Frame + Supplemental Oxygen	Exercise: 15 min sessions, 3 times a day for 10 days. Oxygen: 2 L/min	FEV1: Mean 38±11	30 patients aged 75±7, 54% female
				Gutter Frame + Supplemental Air	Exercise: 15 min sessions, 3 times a day for 10 days. Supplemental Air: 2 L/min	FEV1: Mean 38±15	30 patients aged 75±7, 42% female
				Rollator + Oxygen	Exercise: 15 min sessions, 3 times a day for 10 days. Oxygen: 2 L/min	FEV1: Mean 35±11	30 patients aged 74±8, 57% female
				Rollator + Supplemental Air	Exercise: 15 min sessions, 3 times a day for 10 days. Supplemental Air: 2 L/min	FEV1: Mean 39±10	30 patients aged 74±7, 32% female

Note: ± denotes standard deviation

*: crossover RCT

AECOPD = acute exacerbation of chronic obstructive pulmonary disease; ATS = American Thoracic Society; COPD = chronic obstructive pulmonary disease; ED = emergency department; ERS = European Respiratory Society; FEV1 = forced expiration volume in 1 second; FVC = forced vital capacity; GOLD = global initiative for chronic obstructive lung disease; h = hour; IU = international unit; kcal = kilocalorie; L = liter; min = minute; mj = millijoule; ml = milliliter; MMRC = modified medical research council; NR = not reported; ONS = oral nutrition supplementation; PR = pulmonary rehabilitation; TENS = transcutaneous electrical nerve stimulation; SD = standard deviation; VC = vital capacity; µg = microgram; µmol = micromole

eTable 5. Risk of bias (Cochrane ROB tool) for included studies

Author, Year	Sequence Generation	Allocation Concealment	Blinding of Participants, Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Overall RoB
Austin, 2010[1]	High risk	Unknown	High risk	High risk	High risk	Unknown	High risk	High risk
Basri, 2017[2]	Low risk	Unknown	Low risk	Unknown	Unknown	Unknown	Low risk	Intermediate risk
Behnke, 2000[3]	Unknown	Unknown	High risk	High risk	High risk	Unknown	Unknown	High risk
Borges, 2014[4]	Low risk	Low risk	Unknown	Low risk	High risk	Unknown	Low risk	Intermediate risk
Brown, 1987[5]	Unknown	Unknown	High risk	Unknown	Unknown	Unknown	Unknown	High risk
Cox, 2018 [6]	Low risk	Low risk	High risk	Low risk	High risk	Unknown	Low risk	Intermediate risk
Cross, 2012[7]	Low risk	Low risk	Unknown	Unknown	High risk	Unknown	Low risk	Intermediate risk
Eaton, 2009[8]	Low risk	Unknown	High risk	Low risk	High risk	Unknown	Low risk	High risk
Goktalay, 2013[9]	High risk	Unknown	Low risk	Low risk	High risk	Unknown	High risk	High risk
Greening, 2014[10]	Unknown	Unknown	High risk	High risk	Low risk	Unknown	Low risk	High risk
Greulich, 2014[11]	Low risk	Low risk	High risk	Low risk	High risk	Unknown	Low risk	Intermediate risk
He, 2015[12]	Unknown	High risk	High risk	High risk	Low risk	Unknown	Low risk	High risk
Kirsten, 1998[13]	Unknown	Unknown	High risk	High risk	Low risk	Unknown	Unknown	High risk
Kodric, 2009[14]	Unknown	Unknown	Unknown	Unknown	High risk	Unknown	Unknown	High risk
Kurzaj, 2013[15]	Unknown	Unknown	High risk	Unknown	Unknown	Unknown	Unknown	High risk
Lellouche, 2016[16]	Low risk	Low risk	High risk	Unknown	Low risk	Unknown	Unknown	Intermediate risk
Liao, 2015[17]	Unknown	Unknown	Unknown	Low risk	Low risk	Unknown	Low risk	High risk
Ogasawara, 2018[18]	Low risk	Low risk	Unknown	Unknown	Low risk	Unknown	Low risk	Low risk
Oncu, 2017[19]	Low risk	Unknown	High risk	Unknown	High risk	Unknown	Low risk	High risk
Osadnik, 2014[20]	Low risk	Low risk	High risk	Low risk	Low risk	Unknown	Low risk	Low risk
Pourrashid, 2018[21]	Low risk	Unknown	Low risk	Unknown	High risk	Unknown	Low risk	High risk
Sanjari, 2015[22]	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk	Intermediate risk

Saudny-Unterberger, 1997[23]	Unknown	Unknown	High risk	Low risk	High risk	Unknown	Unknown	High risk
Tang, 2012[24]	Low risk	Low risk	High risk	Low risk	Low risk	Unknown	Unknown	Low risk
Torres-Sanchez, 2017[25]	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Intermediate risk
Torres-Sanchez, 2017[26]	Low risk	Low risk	High risk	Unknown	Low risk	High risk	Low risk	Low risk
Troosters, 2010[27]	Low risk	Unknown	High risk	High risk	High risk	Unknown	High risk	High risk
Tumer, 2009[28]	High risk	Unknown	High risk	High risk	Low risk	Unknown	Unknown	High risk
Vermeeren, 2004[29]	Unknown	Unknown	Low risk	Unknown	High risk	Unknown	Low risk	High risk
Yohannes, 2003[30]	Unknown	Unknown	High risk	High risk	Low risk	Unknown	Unknown	High risk

ROB = risk of bias

eTable 6. Secondary Effectiveness Outcomes in Adult Patients with Exacerbation of COPD

Comparison	Outcome	Findings	Study Design and Sample Size
Airway clearance technique using breathing technique *versus* management without airway clearance technique	Other Symptoms (SGRQ, symptom score) End of Intervention	WMD: -0.02; 95%CI: -3.99 to 3.95, I^2= N/A	1 RCT[7] with 522 patients
	Symptoms BCSS* End of Intervention	WMD: -0.06; 95%CI: -0.56 to 0.44, I^2= N/A	1 RCT[7] with 522 patients
	FEV1% Predicted End of Intervention	WMD: 6.50; 95%CI: -8.46 to 21.46, I^2= N/A	1 RCT[14] with 59 patients
Airway clearance technique using vibration, percussion, or massage *versus* management without airway clearance technique	FEV1% Predicted End of Intervention	WMD: 4.88; 95%CI: -0.37 to 10.12, I^2= 87.37%	2 RCTs[9,15] with 80 patients
	FEV1% Predicted Longest Followup	WMD: 0.00; 95%CI: -5.98 to 5.98, I^2= N/A	1 RCT[9] with 50 patients
	FEV1 Absolute End of Intervention	WMD: 0.00; 95%CI: -0.45 to 0.45, I^2= N/A	1 RCT[9] with 30 patients
		0.9 (SD: 0.5) vs. 0.9 (SD: 0.5), p=non-statistically significant	1 crossover RCT[5] with 24 patients
Airway clearance technique using positive expiratory pressure *versus* management without airway clearance technique	FEV1% Predicted End of Intervention	WMD: -0.30; 95% CI: -4.18 to 3.58, I^2= N/AI^2	1 RCT[20] with 92 patients
	FEV1% Predicted Longest Followup	WMD: -1.30; 95%CI: -7.30 to 4.70, I^2= N/A	1 RCT[20] with 92 patients
	Symptoms BCSS* End of Intervention	WMD: 0.20; 95%CI: -0.91 to 1.31, I^2= N/A	1 RCT[20] with 92 patients
	Symptoms BCSS* Longest Followup	WMD: 0.10; 95%CI: -1.01 to 1.21, I^2= N/A	1 RCT[20] with 92 patients
Exercise using resistance training versus vs management without resistance training	Other Symptoms (Health related Quality of Life, sub scale) End of Intervention	WMD: 5.90; 95%CI: -1.20 to 13.00, I^2= N/A	1 RCT[4] with 46 patients
	Other Symptoms (Health related Quality of Life, sub scale) Longest Followup	WMD: 0.80; 95%CI: -10.31 to 11.90, I^2= N/A	1 RCT[4] with 46 patients
	FEV1% Predicted End of Intervention	WMD: 2.37; 95%CI: -2.83 to 7.57, I^2=0.00%	2 RCTs[4,26] with 106 patients
Exercise using aerobic training versus vs management without aerobic training	FEV1% Predicted End of Intervention	WMD: 0.10; 95% CI: -8.36 to 8.56, I^2= N/A	1 RCT[13] with 29 patients
	FEV1 Absolute End of Intervention	WMD: 0.19; 95% CI: -0.08 to 0.46, I^2= N/A	1 RCT[3] with 46 patients
	Number of steps walked per day End of Intervention	WMD: 663.03; 95% CI: 496.34 to 829.72, I^2= N/A	1 RCT[25] with 58 patients
	30-second sit-to-stand test End of Intervention	WMD: 4.63; 95% CI: 2.54 to 6.72, I^2= N/A	1 RCT[25] with 58 patients

Exercise using combined aerobic + resistance training versus management without exercise training Low Intensity Exercise Group vs management without exercise training	FEV1% Predicted End of Intervention	WMD: -4.80; 95% CI: -13.23 to 3.63, I^2=N/A	1 RCT[24] with 22 patients
	Upper Limb Muscle Strength End of Intervention	SMD: 0.20; 95% CI: -0.70 to 1.00, I^2=N/A	1 RCT[24] with 22 patients
Exercise using combined aerobic + resistance training versus management without exercise training Moderate-to-High Intensity Exercise Group vs management without exercise training	Upper Limb Muscle Strength End of Intervention	p=NS	1 RCT[24] with 22 patients
Chest physiotherapy+exercise (breathing technique+range of motion exercises) combined versus management without exercise training	FEV1% Predicted End of Intervention	WMD: 2.48; 95%CI: -1.81 to 6.77, I^2= N/A	1 RCT[26] with 60 patients
Multi-faceted pulmonary rehabilitation program *versus* management without multi-faceted pulmonary rehabilitation program	Cough (VAS) End of Intervention	WMD: -2.00; 95% CI: -2.98 to -1.02, I^2= N/A	1 RCT[17] with 62 patients
Whole body vibration training during AECOPD *versus* management without whole body vibration	FEV1% Predicted End of Intervention	WMD: -6.52; 95%CI: -16.96 to 3.92, I^2= N/A	1 RCT[11] with 49 patients
Transcutaneous electrical nerve stimulation (TENS) during AECOPD versus Management without Transcutaneous Electrical Nerve Stimulation	FEV1 Absolute End of Intervention	WMD: -0.05; 95%CI: -0.33 to 0.23, I^2= N/A	1 RCT[19] with 82 patients
Dietary intervention using a caloric supplement during AECOPD *versus* usual diet	FEV1% Predicted End of Intervention	WMD: 6.14; 95% CI: -0.76 to 13.04, I^2= N/A	1 RCT[23] with 31 patients
Dietary intervention using a caloric and a protein supplement during AECOPD versus placebo(non-caloric fluid, vanilla flavored water)	FEV1% Predicted End of Intervention	WMD: 0.00; 95% CI: -4.36 to 4.36, I^2= N/A	1 RCT[29] with 47 patients
Dietary intervention using a high fat low carbohydrate diet during AECOPD *versus* usual diet	FEV1 Absolute End of Intervention	WMD: -0.01; 95%CI: -0.31 to 0.29, I^2= N/A	1 RCT[28] with 30 patients
Dietary intervention using vitamin D during AECOPD *versus* placebo	Other Symptoms(SGRQ symptom score) End of Intervention	WMD: -4.47; 95% CI: -8.10 to -0.84, I^2= N/A	1 RCT[21] with 70 patients
	Other Symptoms(SGRQ symptom score) Longest Followup	WMD: -7.19; 95% CI: -11.12 to -3.26, I^2= N/A	1 RCT[21] with 70 patients
	FEV1% Predicted End of Intervention	WMD: 2.20; 95%CI: -7.24 to 11.64, I^2= N/A	1 RCT[22] with 90 patients

BCSS = breathlessness, cough, and sputum scale; CAT = COPD assessment test; CI = confidence interval; CRQ = chronic respiratory disease questionnaire; EQ-5D = EuroQol 5 dimensions; FEV1 = forced expiratory volume in one second; MMRC = modified medical research council scale; MRC = medical research council scale; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias; VAS = visual analog scale; WMD = weighted mean difference

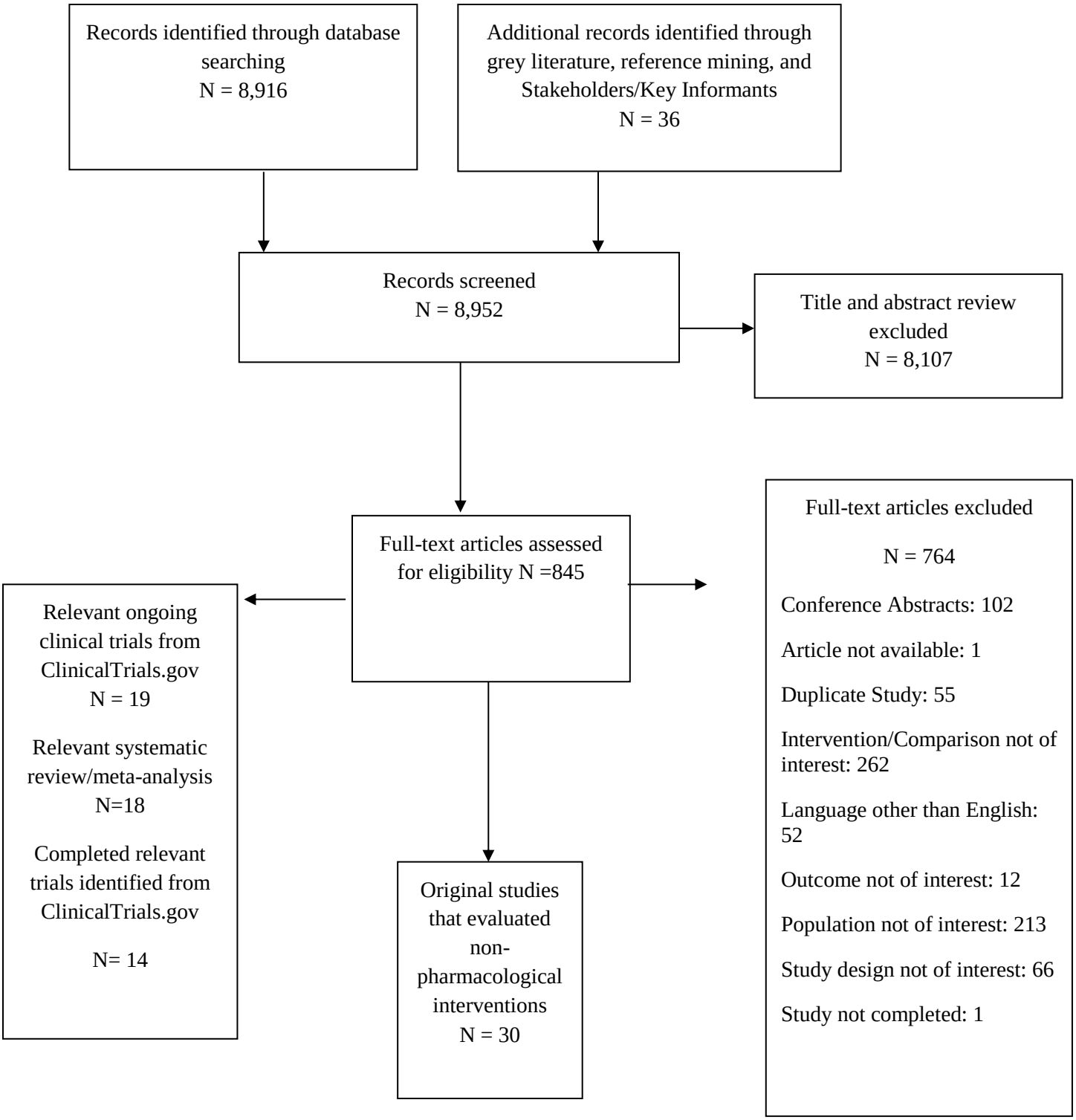
eTable 7. Adverse events and withdrawals

Comparison	Outcome	Findings	Study Design
Airway clearance technique using breathing technique compared with management without airway clearance technique	Withdrawal	OR: 0.94; 95% CI: 0.66 to1.34, I^2=0.00%	2 RCT [7,14]
	Withdrawal due to AE	OR: 0.90; 95% CI: 0.55 to1.48, I^2=0.00%	2 RCT[7,14]
Airway clearance technique using vibration/percussion/massage compared with management without airway clearance technique	Withdrawal	0 events in each arm	1 RCT [5]
Airway clearance technique using chest physiotherapy using positive expiratory pressure compared with management without airway clearance technique	Serious AE	Rate Ratio: 1.50; 95% CI: 0.53 to 4.21, I^2=N/A	1 RCT[20]
	Total number of AEs	Rate Ratio: 1.13; 95% CI: 0.43 to 2.92, I^2=N/A	1 RCT[20]
	Withdrawal	OR: 0.68; 95% CI: 0.20 to 2.32, I^2=N/A	1 RCT[20]
	Withdrawal due to AE	OR: 0.63; 95% CI: 0.17 to 2.42, I^2=N/A	1 RCT[20]
Exercise using resistance training compared with management without resistance training	Withdrawal	OR: 0.72; 95% CI: 0.30 to 1.69, I^2=0.0%	2 RCTs [3,4]
Exercise using combined aerobic + resistance training compared with management without exercise training	Total number of AEs	Rate Ratio: 1.00; 95% CI: 0.14 to 7.10, I^2=N/A	1 RCT[24]
Multi-faceted pulmonary rehabilitation program compared with management without multi-faceted pulmonary rehabilitation program	Infectious AE	Rate Ratio: 1.07; 95% CI: 0.07 to 17.13, I^2=N/A	1 RCT[6]
	General AE	Rate Ratio: 1.07; 95% CI: 0.07 to 17.13, I^2=N/A	1 RCT[6]
	Musculoskeletal AE	Rate Ratio: 1.07; 95% CI: 0.07 to 17.13, I^2=N/A	1 RCT[6]
	Respiratory AE	Rate Ratio: 1.16; 95% CI: 0.53 to 2.54, I^2=N/A	1 RCT[6]
	Serious AE	Rate Ratio: 0.80; 95% CI: 0.28 to 2.32, I^2=N/A	1 RCT[6]
	Total number of AEs	Rate Ratio: 1.03; 95% CI: 0.62 to 1.74, I^2=N/A	1 RCT[6]
	Withdrawal	OR: 1.21; 95% CI: 0.48 to 3.06, I^2=20.79%	2 RCT[6 8]
	Withdrawal due to AE	OR: 1.68; 95% CI: 0.44 to 6.38, I^2=N/A	1 RCT [8]
Whole body vibration training during AECOPD compared with management without whole body vibration	Withdrawal	OR: 0.50; 95% CI: 0.11 to 2.28, I^2=N/A	1 RCT [11]
Transcutaneous electrical nerve stimulation (TENS) during AECOPD compared with vs management without Transcutaneous Electrical Nerve Stimulation	Withdrawal	OR: 0.81; 95% CI: 0.23 to 2.90, I^2=N/A	1 RCT[19]
Gutter frame with supplemental oxygen compared with gutter frame supplemental air	Respiratory AE	Rate Ratio: 0.33; 95% CI: 0.03 to 3.20, I^2=N/A	1 RCT[30]
	Withdrawal	OR: 0.46; 95% CI: 0.78 to 2.75, I2=N/A	1 RCT[30]
	Withdrawal due to AE	OR: 0.22; 95% CI: 0.02 to 2.14, I2=N/A	1 RCT[30]

Comparison	Outcome	Findings	Study Design
	Total number of AEs	Rate Ratio: 0.33; 95% CI: 0.03 to 3.20, I^2=N/A	1 RCT[30]
Rollator with supplemental oxygen compared with gutter frame supplemental air	Respiratory AE	Rate Ratio: 1.00; 95% CI: 0.14 to 7.10, I2=N/A	1 RCT[30]
	Withdrawal	OR: 1.00; 95% CI: 0.13 to 7.61, I2=N/A	1 RCT[30]
	Withdrawal due to AE	OR: 1.00; 95% CI: 0.13 to 7.61, I2=N/A	1 RCT[30]
	Total number of AEs		
Dietary intervention using a caloric supplement during AECOPD compared with usual diet	Withdrawal	OR: 0.39; 95% CI: 0.07 to 2.03, I2=N/A	1 RCT[23]
Dietary intervention using a caloric and a protein supplement during AECOPD compared with Placebo (non-caloric fluid, vanilla flavored water).	Gastrointestinal AE	Rate Ratio: 3.13; 95% CI: 0.33 to 30.09, I2=N/A	1 RCT[29]
	Total AE	Rate Ratio: 3.13; 95% CI: 0.33 to 30.09, I2=N/A	1 RCT[29]
	Withdrawal due to AE	OR: 2.47; 95% CI: 0.54 to 11.37, I2=N/A	1 RCT[29]
Dietary intervention using omega-3 fatty acid compared with standard usual diet.	Withdrawal	OR: 0.22; 95% CI: 0.02 to 2.11, I2=N/A	1 RCT[18]
Dietary intervention using vitamin D during AECOPD compared with placebo.	Withdrawal due to AE	OR: 2.13; 95% CI: 0.61 to 7.43, I2=N/A	2 RCTs[21,22]

AE = adverse event; AECOPD = acute exacerbation of chronic obstructive pulmonary disease; COPD = chronic obstructive pulmonary disease; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

eFigure 1. Flow Chart



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